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Impaired autophagic off-rate causes cardiac aging in progeria mouse model

T. Kamihara¹, Y. Kureishi Bando², K. Nishimura¹, R. Yasheng¹, R. Ozaki¹, T. Murohara¹

¹Nagoya University Graduate School of Medicine, Department of Cardiology, Nagoya, Japan; ²Nagoya University, Nagoya, Japan

Background/Introduction: Aging is known to be one of the primary causes of heart failure. Werner syndrome is one of the aging disorder that caused by dysfunction of DNA helicase-regulatory protein (WRN). However, there is little information whether WRN may cause any specific myocardial remodeling and vulnerability for heart failure. More interestingly, ample evidences demonstrated DNA damage occurred in progeria causes autophagic disorder, contributing to aging phenotype, in short, autophagy may be a guardian of the genome. Although autophagic disorder has been implicated to cause cardiac remodeling in heart failure; however, it remains uncertain whether autophagic disorder may link to the mechanism of aging-induced cardiac remodeling.

Purpose: To elucidate whether autophagic disorder may be mechanistically responsible for cardiac aging we hypothesized whether aging-related DNA injury may affect autophagy that may lead to myocardial remodeling.

Methods: We employed progeria mouse model harboring amino acid (AA) substitution of WRN at position 577 (WRN-K577M), which were evaluated in terms of cardiac function and remodeling at the phase of adult (18 week-old).

Results: WRN-K577M exhibited diffuse left-ventricular (LV) hypertrophy, enhanced fibrosis, and diastolic LV dysfunction with preserved systolic ejection fraction. DNA microarray analysis of WRN-K577M heart revealed that the 253 genes were upregulated compared to age- and gender-

matched wild-type counterpart. Sixteen genes were increased >4 fold higher than wild-type as follows: hypertrophy (Myh7, Klf11), fibrosis (Fgf21, CTGF), inflammatory molecules (Ap1s3, Pla2g2e, Has1, MMP9), and oxidative stress (catalase). Cardiac aging markers (PARP-1, p53 and γ H2AX) increased in heart of WRN-K577M with concomitant increase in oxidative stress (DHE staining) and apoptosis (TUNEL). Notably, autophagic turnover markers (i.e., increased on-rate of autophagy; p62 and LC3-II/I) were increased in myocardium of WRN-K577M, which was refractory to fasting-induced autophagic activation, indicating the on-rate step of autophagy is pathologically augmented under cardiac aging observed in WRN-K577M. In contrast, one of the key regulators of autophagy is the target of rapamycin, TOR kinase, which is the major inhibitory signal that shuts off autophagy with concomitant activation of Akt signaling. In contrast, blockade of the lysosomal fusion into autophagosome by systemic treatment with chloroquine (50 microg/g body weight) reduced LC3-II/I ratio, indicating the retarded off-rate of autophagy mediated by impaired lysosome fusion is presumably responsible for cardiac aging.

Conclusion(s): DNA damage impairs autophagy in heart, leading to myocardial oxidative stress. In WRN-mutant progeria model, off-rate disorder of cardiac autophagy is, at least in part, the cause of increase in oxidative stress and inflammation in heart leading to HFpEF.